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A Phase IB Dose-Escalation Study of the HSP90 Inhibitor SNX-5422 and Erlotinib in Patients with EGFR-Mutant Lung Cancer and Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

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BACKGROUND

- Heat shock protein 90 (Hsp90) is a molecular chaperone that is exploited by cancer cells for at least two purposes:
  - To activate and stabilize labile forms of oncoproteins, including many kinases and transcription factors, that have undergone biochemical transformations (mutation, translocation, amplification, overexpression); and
  - To act as a buffer against the cellular stresses essential for cancer cell survival.[1]
- Hsp90 inhibition has shown clinical activity in cancers addicted to particular driver oncogenes, such as HER2, EML4-ALK, and mutant epidermal growth factor receptor (EGFR).[1]
- SNX-5422 is an orally bioavailable prodrug of SNX-2112, which is a highly potent, non-geldanamycin analog Hsp90 inhibitor.[2,3] SNX-5422 has extended tumor residence time and has demonstrated significant antitumor activity in multiple mouse xenograft models of human tumors.[2,4,5]
- Erlotinib is a tyrosine kinase inhibitor used in the treatment of locally advanced or metastatic EGFR-mutant non-small cell lung cancer (NSCLC).[6]
- In cellular models of mutant EGFR (L858R and T790M mutations), SNX-2112 alone and in combination with erlotinib inhibited EGFR activation of pAKT and pSTAT3.[7] In NCI-H1975 xenograft models, SNX-5422 showed activity as a single agent (Figure 1) and in combination with erlotinib (Figure 2).[7]

Figure 1. SNX-5422 Activity in NCI-H1975 Xenograft Models*

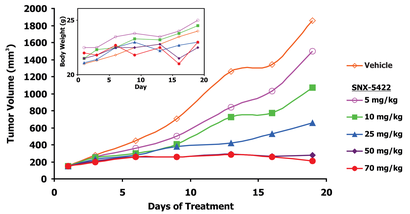
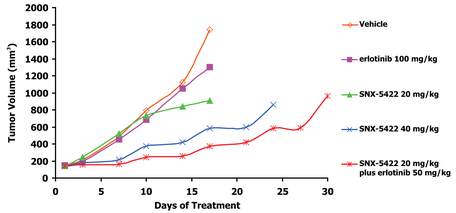


Figure 2. SNX-5422 + Erlotinib Activity in NCI-H1975 Xenograft Models*



* Adapted from Rice 2009 (reference 7)

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OBJECTIVES

Primary

- To determine the maximally tolerated dose (MTD) of SNX-5422 when given in combination with erlotinib in patients with EGFR-mutant NSCLC with acquired resistance to erlotinib.

Secondary

- To characterize the safety profile for the combination of SNX-5422 and erlotinib.
- To investigate the effects of SNX-5422 plus erlotinib on tumor response.

METHODS

Study Design

- Phase 1, multicenter, open-label, 3+3 dose-escalation study
- SNX-5422 dosing was started at 50 mg/m², with an escalation schedule of 75 mg/m² and 100 mg/m², depending on patient tolerability. The actual dose administered was based on body surface area, calculated via actual body weight at the start of each cycle. The calculated dose was then rounded to nearest mg on the dosing chart. SNX-5422 was available in 5, 20, 75, and 150 mg capsules.
- Erlotinib dosing ranged from 25-150 mg once daily. Erlotinib was available as 25, 100, and 150 mg tablets.
- Ophthalmological examinations (visual field, visual acuity, ophthalmoscopy, Optical Coherence Tomography, dark adaptation using an SST-1 adaptometer) were conducted at Screening, end of Cycle 1, and study end.

Dosing Schedule

- Each cycle = 28-day period
- SNX-5422: Once daily by mouth every other day (QOD) in the morning for 21 days (total of 11 doses) followed by a 7-day drug-free period
- Erlotinib: Once daily by mouth every day (QD) in the evening for 28/28 days

Key Inclusion Criteria

- Males or non-pregnant, non-breastfeeding females ≥18 years-of-age with pathologic evidence of advanced lung adenocarcinoma (stage IIIB/IV) confirmed histologically/cytologically and an activating mutation in the EGFR gene (e.g., G719X, exon 19 deletion, T790M, L858R, L861Q).
- Progressed on treatment with erlotinib/gefitinib, and received no more than 4 prior lines of cytotoxic chemotherapy, including erlotinib/gefitinib.
- Karnofsky performance score ≥70, adequate baseline laboratory values, and all adverse events (AEs) recovered to at least ≤Grade 1 toxicity level.

Key Exclusion Criteria

- CNS metastases that were symptomatic and/or required escalating doses of steroids.
- Current use, or use within the past 28 days or 5 half-lives of anticancer therapy, whichever was shorter, before study entry (except erlotinib/gefitinib within 4 weeks was allowed).
- Conventional chemotherapy, radiation, or monoclonal antibodies within 4 weeks before study entry.
- Gastrointestinal (GI) diseases or conditions (including chronic diarrhea) affecting drug absorption (including gastric bypass) or safety assessments (e.g., Crohn's disease, irritable bowel syndrome).
- Glaucoma, retinitis pigmentosa, macular degeneration, or any retinal changes detected by ophthalmological examination.

Safety and Efficacy Analysis

- Adverse event data, laboratory parameters, ECG, vital signs, ophthalmological examination.
- Tumor response was assessed every 8 weeks using RECIST 1.1 criteria for solid tumors. Only patients with post-baseline disease assessment data were included in the tabulation of best response to treatment.

RESULTS

Table 1. Baseline Characteristics

Parameter	N=17
Age, median (range), years	67 (37-81)
Age >65 years, n (%)	9 (53%)
Males, n (%)	14 (82%)
Race, n (%)	
White	13 (76%)
Asian	3 (18%)
Unknown[1]	1 (6%)
Prior systemic therapy, number of regimens, n (%)	
1	3 (18%)
2	4 (24%)
3	3 (18%)
4	3 (18%)
5	4 (24%)

[1]Patient refused to answer.

Table 2. SNX-5422 Dosing Cohorts

Cohort	SNX-5422 Dose (mg/m²)	Number of Patients Assigned to Cohort (N=17)	DLT (Cycle 1)
1	50	10	
2	75	7	n=2 (diarrhoea)

Maximum Tolerated Dose

- Dose escalation above 50 mg/m² was unsuccessful — at 75 mg/m² QOD, 2 patients experienced DLTs (diarrhoea in both cases).
- The MTD, therefore, was defined at 50 mg/m² QOD, and Cohort 1 was expanded.

Dose Limiting Toxicities (DLTs)

- 2 patients had DLT of diarrhoea, one Grade 4 and one Grade 2; both SAEs resolved when drug was held.

Table 3. Summary of Adverse Events

Adverse Event (AE)	Number of Patients (%) N=17
At least one treatment-emergent AE	17 (100%)
Treatment-related AE	17 (100%)
Grade 3 or 4 treatment-emergent AE	6 (35%)
Grade 5 AE (death)	0
Serious AE (SAE)	6 (35%)
Treatment-related SAE[1]	2 (12%)
AEs leading to study discontinuation[1]	1 (6%)
AEs leading to dose interruption[2]	5 (29%)
Dose-limiting toxicity[1]	2 (12%)

[1]Diarrhoea. [2]Diarrhoea was the cause of dose interruption in 4 of these patients.

Table 4. Most Frequent[1] Combination Treatment, Treatment-Related Adverse Events (AEs)

Combination Treatment, Treatment-Related AE	50 mg/m² (n=10)		75 mg/m² (n=7)		Total (N=17)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
	Number of Patients		Number of Patients		Number of Patients	
Diarrhoea	8	1	6	1	14	2
Fatigue	8	0	5	0	13	0
Nausea	6	0	3	0	9	0
Rash[2]	6	0	3	0	9	0
Dry eyes[2]	3	0	2	0	5	0
Fissures[2]	4	0	0	0	4	0
Anorexia	3	0	0	0	3	0
Vomiting	1	0	1	0	2	0
GORD	1	0	1	0	2	0
Flatulence[2]	1	0	1	0	2	0
Paronychia[2]	1	0	1	0	2	0
Visual changes[3]	1	0	0	0	1	0
Blurred vision[3]	1	0	0	0	1	0
Visual disturbance[3]	0	0	1	0	1	0
Nictalopia[3]	0	0	1	0	1	0

GORD = gastrooesophageal reflux disease. [1]Reported by ≥2 patients in total. [2]Typical AEs associated with erlotinib use. [3]No abnormalities observed during ophthalmological examination; events reported only after direct questioning with regard to vision (not spontaneously reported).

Antitumor Activity

- Antitumor activity could be assessed in 15 patients for 2 cycles and in 14 patients for more than 2 cycles (2 patients withdrew consent in Cycle 1 and 1 patient withdrew consent in Cycle 3.)
- No objective responses were observed.
- Stable disease was observed as best response in 9 of 15 patients (60%), and 6 of 14 patients (43%) had stable disease at the end of 4 months.
- Noteworthy stable disease was observed in 2 patients (14%) having stable disease for at least 9 months and are ongoing. Both patients were taking 50 mg/m² SNX-5422; erlotinib was dosed at 100 mg in 1 patient and 50 mg (then reduced to 25 mg) in the other patient.
- Another patient on 50 mg/m² SNX-5422 + 100 mg erlotinib had decreases in target lesions of 13% and 18% at the end of 2 and 4 months, respectively, but had increased brain metastases at the end of 5 months, which necessitated radiation therapy.

CONCLUSIONS

In patients with acquired resistance to erlotinib:

- The MTD of SNX-5422 was established at 50 mg/m² in combination with erlotinib.
- SNX-5422 at doses up to 50 mg/m² was generally well-tolerated when combined with erlotinib.
- Diarrhoea was the most common AE during SNX5422 + erlotinib combined therapy, and the cause of DLT.
- SNX-5422 in combination with erlotinib showed promising signs of clinical activity in patients with EGFR-mutant NSCLC, with an 18% decrease from baseline in target lesions in Cycle 4 in 1 patient and stable disease for at least 9 months in 2 patients (14%).

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